

REMARKS

Prior to this amendment, claims 1-7 and 11-37 were pending in the application.

Claims 2-13, 15, and 17-21 are cancelled by this amendment. Claims 14, 16, and 28-37 are previously presented and allowed. Claims 1 and 23-27 are currently amended.

New claims 38-78 are added by this amendment. The amended claims and new claims are fully supported by the specification and/or the claims as filed and do not add new matter. Specific support for each of the amended and new claims is set forth below:

Claim	Support
1	page 4, lines 5-7; page 7, lines 13-14, 23-26
22-27	Amended to remove dependency to cancelled claim
38	page 4, lines 5-6
39	page 3, line 26 to page 4, line 2
40	page 3, lines 26-27
41	page 4, lines 8-10
42-43	page 4, lines 17-22
44	page 7, line 10
45	page 7, lines 15-18
46	page 7, lines 20-22
47-56	page 4, lines 17-22

Claim	Support
57	page 7, lines 23-24
58	page 4, lines 5-6
59	page 4, lines 8-10
60-69	page 4, lines 17-22
70	page 7, lines 13-14
71	page 7, lines 15-16
72	page 7, lines 17-18
73	page 7, line 19
74	page 7, lines 20-21
75	page 7, line 22
76	page 7, lines 23-24
77	page 7, lines 25-26
78	page 7, line 27

Applicants thank the Examiner for the courtesies extended in the telephone interview of August 11, 2005 and for considering and commenting on the current claim amendments. Applicants respectfully request reconsideration of the claims in light of the amendments made.

The Claimed Invention

The claimed invention is directed to compositions comprising an osteogenic protein, an injectable hyaluronic acid ester, and either *no pore former* or a pore former selected from a *liquid pore former* or *sodium bicarbonate*. The compositions must be *injectable through the skin of a patient* to allow for cartilage or bone repair without the open reduction procedure necessary with implantable devices.

The Cited Art

Valentini refers to the use of *solid*, porous, degradable hyaluronic acid scaffolds, which may incorporate biologically active molecules such as BMP. The Valentini scaffolds are described as useful for medical purposes—including tissue repair, reconstruction, and wound healing. (Abstract and Col 1, lines 64-67.) Essentially, the Valentini solid scaffold is intended for *implantation* at a location needing repair such that the interconnecting pores of the scaffold permit cells to grow into and eventually replace the scaffold. (Col. 4, II. 30-35.)

Although Valentini does state that “the porous scaffolds of the invention can be fabricated to any size or shape and can be produced to virtually any desired predetermined pore size, depending upon the application (Col. 2, lines 7-10; see also Col 4, lines 35-38), Valentini specifically recites only the following pore formers (Col. 6, lines 4-15):

salt crystals such as NaCl, KCl, MgCl₂, CaCl₂, and BaSO₄; soluble proteins such as albumin, globulins, and the like; soluble dextrans such as dextran and dextransulfates, and the like; soluble hydrogels such as agarose, alginate, chitosan, cellulose, carboxymethylcellulose, and the like; and microspheres of polylactic acid, polyglycolic acid, and the like.

Valentini does not teach or suggest that the disclosed scaffolds can be produced *without* pore formers. Nor does Valentini teach or suggest the use of *liquid* or *sodium bicarbonate* pore formers. Further, Valentini does not provide any teaching or suggestion to modify its compositions to render them *injectable*. Accordingly, nothing in Valentini suggests the use of liquid pore formers or sodium bicarbonate or no pore former at all to produce an injectable composition.

Although the process of making the Valentini scaffolds includes a step during which the composition is in a thick slurry form of liquid intermediate, nothing in Valentini suggests using this intermediate for any purpose other than to produce the final solid scaffold. Similarly, nothing in Valentini suggests modification of this intermediate in any way to make it useful for another purpose, and particularly not in such a way as to render it capable of being injected through the skin of a patient.

Pheulpin is directed to a conically walled *syringe* for use in *dentistry* for injection of composites, cements and medicated pastes and the like *into cavities*. Pheulpin does not teach or suggest the administration of pharmaceutical compositions through the skin of a patient. Nor does Pheulpin provide any information about what properties a composition must possess in order for it to be injectable.

Langen is directed to an *apparatus* for injecting *meat* with a substance having a paste-like consistency (such as a curing fluid). This device is not suitable for therapeutic injections of pharmaceutical formulations through the skin of a patient.

Phillips is directed to a disposable injection *apparatus* for delivery of a cream medicament into an animal. It is designed to prevent the need for cleaning a chamber after every use. Phillips does not provide any information regarding the substances to

be injected other than the very general statement that it may be a medicament in the form of a cream or paste. Phillips does not describe any properties that a cream or paste must possess in order to render it suitable for injection—particularly through the skin of a patient.

Pheulpin, Langen, and Phillips are non-analogous art and are not properly combined with Valentini. Moreover, even if this weren't the case, nothing in these three references addresses the deficiency in Valentini. Nothing in these three references provides any suggestion to modify the compositions of Valentini to remove pore formers or to include liquid pore formers or sodium bicarbonate or otherwise render the compositions injectable.

35 U.S.C. § 103 - Obviousness

Claims 6, 15, and 19 stand rejected as allegedly obvious over Valentini in view of Pheulpin, Langen, and Phillips, and in further view of Wozney. These claims have been cancelled without prejudice, removing the basis for this rejection. The Examiner has also rejected claims 1-5, 7, and 11-13, and 17-27 as allegedly obvious over Valentini in view of Pheulpin, Langen, and Phillips. Claims 2-5, 7, 11-13, and 17-21 have been cancelled and claims 1 and 23-27 have been amended. Applicants traverse the rejection.

To establish a case of *prima facie* obviousness, the Examiner must show that:

- (1) the prior art reference (or references when combined) teach or suggest all the limitations of the claims; (2) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a reference or to combine teachings; and (3) there is a reasonable

expectation of success of achieving the claimed invention. *Manual of Patent Examining Procedure*, § 2143. Applicants note that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure. *Id.*

(1) Valentini does not teach or suggest all the limitations of the pending claims

Valentini does not teach or suggest compositions that are injectable *through the skin* of a patient. More specifically, Valentini does not teach or suggest compositions without pore formers or compositions comprising liquid pore formers or sodium bicarbonate pore formers. Because the clearly stated objective of Valentini is to create solid scaffolds with large, thin walled pores, all of Valentini's compositions (including intermediate compositions) contain pore formers. Valentini's suggestions for suitable pore formers are limited to salt crystals, soluble proteins, soluble dextrans, hydrogels, and microspheres. None of these suggested pore formers is a liquid pore former or sodium bicarbonate.

Furthermore, even when Valentini is combined (albeit improperly) with the teachings of Pheulpin, Langen, and Phillips, there is still no teaching or suggestion of the compositions as claimed. The three secondary references certainly do not suggest modifications of the Valentini compositions to eliminate the pore former or to replace one of the suggested pore formers with a liquid pore former or sodium bicarbonate. In fact, they do not describe or suggest any properties of injectable compositions at all.

Therefore, in order to reach the claimed invention from the teachings of Valentini, there must be some motivation within Valentini itself to modify its disclosed

compositions to render them injectable through the skin of a patient. More specifically, there must be some motivation within Valentini itself to either remove the pore formers from the compositions or to replace the pore formers discussed in Valentini with a liquid pore former or sodium bicarbonate.

(2) There is no motivation or suggestion to modify Valentini's compositions to reach the claimed invention

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *Manual of Patent Examining Procedure*, § 2143.01. Thus, there are three permissible sources for a motivation to combine prior art references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Id.* And more importantly, the motivation to modify a reference cannot come from the Applicant's own disclosure. *Sensonics Inc. v. Aerasonic Corp.*, 81 F. 3d 1566, 38 U.S.P.Q. 2d 1551 (Fed. Cir. 1996).

As noted above, in order to prepare a composition of the claimed invention, the Valentini compositions must be modified to either eliminate the pore former or to replace the Valentini-suggested pore formers with a liquid pore former or sodium bicarbonate. Because none of the secondary references suggest such a modification, the motivation to make this replacement must be found in Valentini itself, in the nature of the problem

to be solved (i.e., tissue repair or reconstruction), or in the knowledge of one of skill in the art.

It is evident that Valentini on its face provides no such motivation. The clearly articulated goal of the Valentini patent is to produce a solid scaffold for *implantation* to promote tissue repair or wound healing. To promote cell ingrowth, this scaffold must have large pores, i.e., pores that are produced by pore formers during preparation of the final scaffold. In other words, pores are an essential feature of Valentini's compositions. Therefore, Valentini provides no motivation for, and in fact, teaches away from, modifying its compositions to exclude pore formers.

In addition, Valentini provides no motivation to use a liquid pore former or sodium bicarbonate as a pore former. Valentini provides a broad list of suitable pore formers, ranging from salt crystals to microspheres of polyglycolic acid. However, the use of pore formers in a liquid form and the use of sodium bicarbonate are not included in this list. Upon reading Valentini, one of skill in the art would have no motivation to look beyond the broad classes of pore formers suggested in column 6 and select a non-suggested pore former—particularly one that would render the composition suitable for injection through the skin of a patient, such as a liquid pore former or sodium bicarbonate.

Moreover, the motivation to replace (or eliminate) the pore formers listed in Valentini to achieve an injectable formulation is not present in the nature of the problem to be solved or the knowledge in the art. Valentini does not suggest that there is any problem or deficiency with its *implantable* scaffolds. Nor does Valentini suggest any advantage to producing injectable scaffolds. In fact, nothing in Valentini suggests that

any of its scaffolds (or intermediates) could even be prepared as injectable formulations of osteogenic proteins. Valentini is very clearly directed to providing solid scaffolds with large pores to promote cell ingrowth upon *implantation* and with thin walls to allow for degradation over time. Valentini itself suggests that this purpose is best achieved with significant amounts of large pore formers. (Col. 8, Table 1.) One of skill in the art would believe that the Valentini product would not function for its intended purpose in the absence of pore formers and thus, would not be motivated to eliminate pore formers from the Valentini composition. Furthermore, without a goal of providing injectable formulations in the first place, one of skill in the art would have no motivation to move beyond the extensive and broad list of pore formers listed in Valentini to select non-listed liquid pore formers or sodium bicarbonate—pore formers that were specifically selected for the present invention because they produce injectable formulations.

Thus, there is no motivation present in Valentini itself, the knowledge in the art, or the problem to be solved to modify the Valentini compositions to reach the claimed invention.

(3) One of skill in the art would not have a reasonable expectation of success in modifying Valentini's compositions to reach the claimed invention

Because Valentini does not teach the claimed compositions and provides no suggestion how to modify them to reach the claimed invention, one of skill in the art would have no expectation of success in making a composition without pore formers or with liquid pore formers or sodium bicarbonate that would be capable of injection through the skin of a patient. Valentini provides no teaching as to when or why to vary the amounts or ratios of pore formers to achieve compositions with different properties.

Valentini only specifically describes the amount and ratio of the pore former NaCl suitable for generating solid scaffolds with thin, interconnecting pores. As Dr. Kim has previously testified, the Valentini intermediate compositions comprising NaCl is not pharmaceutically acceptable and thus cannot be injected through the skin of a patient. Likewise, the final scaffold made by Valentini using NaCl as the pore former is not injectable because it is a solid or semi-solid composition. Accordingly, one of skill in the art, following Valentini's teachings, would have no expectation that the Valentini compositions could successfully be injected through the skin of a patient.

Applicants respectfully submit that the Examiner has not established a case of *prima facie* obviousness. Valentini, alone or combined with Pheulpin, Langen, and Phillips, does not render the claims obvious because it does not teach or suggest the injectable compositions of the claimed invention. None of the cited documents disclose an injectable composition comprising an osteogenic protein, an injectable hyaluronic acid ester, and either no pore former at all, or a pore former selected from liquid pore formers and sodium bicarbonate. None teaches or suggests that modifying the non-injectable composition of Valentini by removing the pore former or replacing it with sodium bicarbonate or a liquid pore former will render it injectable. And none provides a motivation to do so or a reasonable expectation of success. Accordingly, Applicants request that the rejection under 35 U.S.C. § 103 be withdrawn.

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In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

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